Attorney Docket No. BULK 3.0-018

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al.

Application No.: 10/601,844 — Group Art Unit: 1624

Filed: June 23, 2003 — Examiner: Paul V. Ward

For: AMORPHOUS LEVOCETIRIZINE DIHYDROCHLORIDE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

BRIEF ON APPEAL

Further to the Notice of Appeal that was submitted on March 21, 2008, this brief is submitted in support of the appeal.

1. Real Party in Interest

The real parties in interest are Dr. Reddy's Laboratories Limited and Dr. Reddy's Laboratories, Inc., assignees of the application from the inventors.

2. Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal, or which will affect or have a bearing on this appeal.

3. Status of the Claims

Claims 1-22 and 24-37 are pending. Following a final restriction requirement, claims 19-22 and 24-37 were withdrawn from consideration and have not been examined. Claims 1-18 were examined, were finally rejected in the Office Action dated May 24, 2007 ("Final Rejection"), and are the subject of this appeal. The pending

claims are appended hereto, including prior amendments and with the canceled and withdrawn claims identified.

4. Status of Amendments

No amendment was submitted after the Final Rejection. Other amendments that were submitted during prosecution have been entered.

5. Summary of the Claimed Subject Matter

Independent claims 1-3 are directed to amorphous levocetirizine dihydrochloride, a drug compound having antihistaminic activity. Claim 2 specifies that the compound is substantially free from crystalline forms of the drug, and claim 3 specifies a particular X-ray powder diffraction pattern for the compound.

Independent claim 4 is directed to a pharmaceutical composition containing amorphous levocetirizine dihydrochloride.

Independent claim 6 is directed to a composition containing solid levocetirizine dihydrochloride, wherein at least 80% by weight of said levocetirizine dihydrochloride is in an amorphous form.

The remaining claims are dependent from an independent claim, and add limitations thereto.

6. Grounds of Rejection to be Reviewed on Appeal

A. Whether claim 3 is indefinite for referring to a drawing figure.

B. Whether claims 2 and 10 are indefinite for their inclusion of the modifying word “substantially.”

C. Whether claims 1-16 are anticipated by teachings from any of the cited documents Tang et al. (*J. China Pharm. Univ.*, 2002), Pflum et al. (*Organic Process Research and Development*, 2001), and Van de Venne et al. (U.S. Patent No. 6,489,329).

D. Whether claims 17 and 18 are rendered obvious by teachings from Van de Venne et al. (U.S. Patent No. 6,489,329).

7. <u>Argument</u>

<u>A. Rejection of Claim 3 Under 35 U.S.C. § 112</u>

Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because it refers to Figure (1) of the application.

According to MPEP § 2173.05(s):

> Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

Consistent with MPEP § 2173.05(s), incorporation by reference of Figure (1) into claim 3 is necessary because doing so is more concise than duplicating the X-ray diffraction pattern into the claim, and it is not feasible to reduce the diffraction pattern into words. Further, incorporation by reference of X-ray diffraction patterns into patent claims is a standard practice in pharmaceutical and other chemically-oriented patents, as has been pointed out by the appellants in a response with reference to U.S. Patent Nos. 7,148,231, 7,074,928, 7,060,712, 7,015,238, 6,998,503, 6,958,337, and 6,900,221, all of which have claims with a format similar to that of rejected claim 3. Accordingly, Appellants respectfully submit that the rejection is not proper and should be reversed.

<u>B. Rejection of Claims 2 and 10 Under 35 U.S.C. § 112</u>

Claims 2 and 10 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because they recite the relative term "substantially." According to the Examiner, the term "substantially" is not defined by the claim, the specification does not provide an appropriate standard, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

According to MPEP 2173.05(b):

> The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim

> indefinite under 35 U.S.C. 112, second paragraph. *Seattle Box Co., v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification.

Appellants submit that, contrary to the Examiner's position, one skilled in the art would have no difficulty ascertaining the scope of the claimed subject matter in light of the specification. The paragraph bridging pages 7 and 8 of the instant specification clearly delineates the scope of "substantially free of crystalline forms" recited in claims 2 and 10. Appellants respectfully request reversal of this rejection.

C. <u>Rejection of Claims 1-16 Under 35 U.S.C. § 102</u>

Claims 1-16 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Tang et al. (*J. China Pharm. Univ.*, *22*(4): 311-2, 2002; "Tang"), Pflum et al. (*Organic Process Research and Development*, *5*(2): 110-115, 2001; "Pflum"), and Van de Venne et al. (U.S. Patent No. 6,489,329; "Van de Venne"). According to the Examiner, Tang and Pflum teach the exact amorphous levocetirizine that falls within the range of the appellants' compound. Van de Venne was asserted as teaching compositions comprising levocetirizine dihydrochloride that falls within the range of the appellants' compound with one or more pharmaceutically acceptable excipients.

According to MPEP § 2131:

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 638, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Contrary to the Examiner's position, Tang does not disclose a compound having each and every limitation as set forth in claims 1-3 of the instant application. Claims 1-3 are directed to <u>amorphous</u> levocetirizine dihydrochloride. Although the English portions of Tang apparently disclose an isolation of levocetirizine hydrochloride by high performance liquid chromatography, there is no teaching or suggestion that the isolated levocetirizine hydrochloride was in a solid form, or was amorphous. Similarly, although

Pflum discloses an enantiomeric synthesis of levocetirizine dihydrochloride, it does not teach or suggest that the resulting levocetirizine dihydrochloride was amorphous.

With regard to Van de Venne, while the appellants agree that the reference discloses compositions comprising levocetirizine dihydrochloride with one or more pharmaceutically acceptable excipients, they are not the same compositions as recited in claims 4-16. Claims 4-16 are directed to a pharmaceutical composition comprising amorphous levocetirizine dihydrochloride and one or more pharmaceutically acceptable excipients. As with Tang and Pflum, there is no teaching or suggestion that the levocetirizine dihydrochloride was amorphous. Appellants note that the Examiner apparently would not argue with this conclusion, as the Final Rejection at page 3 states that "Van de Venne teaches compositions comprising levocetirizine dihydrochloride," with the term "amorphous" conspicuously absent.

Appellants submit that it was error to give no weight to the claim element "amorphous." *See Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989) ("The identical invention must be shown in as complete detail as is contained in the ... claim."). Because Tang, Plum, and Van de Venne do not disclose amorphous levocetirizine dihydrochloride, claims 1-16 are clearly not anticipated, and reversal of this rejection is respectfully requested.

D. Rejection of Claims 17 and 18 Under 35 U.S.C. § 103

Claims 17 and 18 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Van de Venne. According to the Examiner, Van de Venne teaches compositions comprising levocetirizine dihydrochloride, and it was acknowledged that the reference fails to disclose the claimed moisture content. However, according to the Examiner, it would have been obvious to one skilled in the art at the time of the invention to obtain the claimed composition because obviousness based on similarity of structure and function entails motivation to make the claimed compound in expectation that compounds similar in structure will have similar properties. According to the Examiner, the amorphous form is an obvious variation which one is motivated to obtain because of the expected solubility advantages (quoting from Hancock et al.,

Pharmaceutical Research 17:397-404 (2000)). Appellants cannot agree with this conclusion.

As stated in MPEP § 706.02(j):

> "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

Thus, to sustain the rejection of obviousness, the prior art should provide the limitations of claims 17 and 18. Claims 17 and 18 are directed to a pharmaceutical composition comprising amorphous levocetirizine dihydrochloride and one or more pharmaceutically acceptable excipients, and having a certain moisture content. As discussed above with respect to the § 102 rejection, Van de Venne fails to teach or suggest amorphous levocetirizine dihydrochloride, and has no information concerning the desirability of the claimed moisture content.

Appellants also submit that, contrary to the assertion of the Office, the skilled artisan would not have been motivated to modify Van de Venne to obtain amorphous levocetirizine dihydrochloride for use in a pharmaceutical composition with a reasonable likelihood of success. This is particularly true, given the fact that amorphous levocetirizine dihydrochloride had not been described, prior to publication of the appellants' application. Notwithstanding the fact that amorphous compounds might tend to be more soluble than their crystalline counterparts, it remains the case that the pharmaceutical industry still faces significant challenges in the identification and isolation of amorphous pharmaceutical compounds. As explained by O. Almarsson and C. R. Gardner, "Novel Approaches to Issues of Developability," *Current Drug Discovery,* January 2003, pp. 21-26, a copy of which is appended hereto:

> Amorphous compounds carry inherent risks due to their physicochemical nature. In addition to being physically meta-stable (ie, prone to physical form changes such as crystallization), amorphous forms are generally less chemically stable in the solid state than the crystalline form. Amorphous compounds also tend to have very low bulk

> densities, making the materials difficult to isolate and handle. They also exhibit irregular particle properties and their high surface area often results in hygroscopicity (excessive moisture-sorption). These properties, despite presenting a potentially surmountable set of issues in discovery and early development, can cause major challenges in late-stage development.
>
> In general, pharmaceutical companies make every effort to avoid committing to the development of an amorphous compound… As has already been stated, amorphous forms have, in rare cases, been chosen for development despite the risk of crystallization, an event that could cause a product to fail its critical performance criteria and regulatory specifications. The results of such an occurrence are disastrous for development programs, especially in late-stage trials where the formulation used is that intended for the market.

Other recent articles have reported various aspects of the phenomenon of pharmaceutical compound polymorphism. Among these is A. Goho, "Tricky Business," *Science News*, Vol. 166, pages 122-3 (August 21, 2004), and an eight-page website reprint of this article is appended. Those skilled in the art are aware from this and other publications that: it is not possible to predict whether a particular compound has more than one polymorphic form; it is not possible to predict the number of polymorphic forms of a compound that will be discovered; and there is no predictable way to proceed toward preparing a new form of a compound. The article also reports that seemingly minor alterations to a process can give rise to the formation of a previously unknown polymorphic form.

Based on the foregoing, the appellants submit that one of ordinary skill in the art cannot predict with any certainty whether the amorphous form of a crystalline compound might be isolated without undue experimentation, even if motivation existed. Similarly, one of ordinary skill in the art cannot predict with any certainty that the existence of a crystalline form of a compound necessarily indicates the possible existence of a stable amorphous form of the same compound. Obviousness of claims 17 and 18 is simply not possible, absent hindsight in view of the appellants' disclosure.

Accordingly, claims 17 and 18 were not rendered *prima facie* obvious by any teaching in Van de Venne, and reversal of this rejection is respectfully requested.

CONCLUSION

The rejections made under 35 U.S.C. §§ 112, 102, and 103 have all been shown to be improperly founded. Each of these rejections should now be reversed, and such action is respectfully solicited.

Respectfully submitted,

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May 20, 2008

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CLAIMS APPENDIX

1. Amorphous levocetirizine dihydrochloride.

2. Amorphous levocetirizine dihydrochloride, which is substantially free of crystalline forms of cetirizine dihydrochloride.

3. Amorphous levocetirizine dihydrochloride characterized by an X-ray powder diffraction pattern substantially in accordance with Figure (1).

4. A pharmaceutical composition comprising a prophylactically or therapeutically effective amount of amorphous levocetirizine dihydrochloride and one or more pharmaceutically acceptable excipients.

5. The pharmaceutical composition of claim 4, which is substantially free of crystalline forms of cetirizine dihydrochloride.

6. A composition comprising levocetirizine dihydrochloride as a solid, wherein at least 80% by weight of said levocetirizine dihydrochloride is in an amorphous form.

7. The composition of claim 6, wherein at least 90% of said solid levocetirizine dihydrochloride is in an amorphous form.

8. The composition of claim 6, wherein at least 95% of said solid levocetirizine dihydrochloride is in an amorphous form.

9. The composition of claim 6, wherein at least 99% of said solid levocetirizine dihydrochloride is in an amorphous form.

10. The composition of claim 6, which is substantially free of crystalline forms of cetirizine dihydrochloride.

11. The composition of claim 6, wherein at least 1% of said solid levocetirizine dihydrochloride is in a crystalline form.

12. The composition of claim 6, wherein at least 5% of said solid levocetirizine dihydrochloride is in a crystalline form.

13. The composition of claim 6, which is a pharmaceutical composition.

14. The composition of claim 13, further comprising one or more pharmaceutically acceptable excipients.

15. The composition of claim 13, wherein said pharmaceutical composition is a solid dosage form for oral administration.

16. The composition of claim 15, wherein said solid dosage form is a tablet.

17. The composition of claim 6 having a moisture content ranging from about 0.3% to about 12% by the KF method.

18. The composition of claim 6 having a moisture content ranging from about 1.5% to about 7.5% by the KF method.

19. (Withdrawn) A process for the preparation of amorphous levocetirizine dihydrochloride, which comprises

a) providing levocetirizine free base or salt thereof in a solvent carrier;

b) treating said levocetirizine in said carrier with hydrochloric acid to form a dihydrochloride salt of cetirizine in solution;

c) removing said solvent carrier to obtain a residue;

d) adding a liquid hydrocarbon compound to said residue to separate said amorphous levocetirizine dihydrochloride as a solid mass.

20. (Withdrawn) The process of claim 19, further comprising isolating said solid mass.

21. (Withdrawn) The process of claim 20, further comprising removing unbound solvent from said isolated solid mass to obtain a substantially dry form of said amorphous levocetirizine dihydrochloride.

22. (Withdrawn) The process of claim 21, wherein said step of removing said unbound solvent comprises drying said solid mass at a temperature of from about 60 to about 110 degrees Celsius.

23. (Canceled)

24. (Withdrawn) The process of claim 19, wherein said liquid hydrocarbon compound is selected from the group consisting of toluene, xylene, cyclohexane, and heptane.

25. (Withdrawn) The process of claim 19, wherein said solvent carrier is selected from the group consisting of a ketone solvent, an aqueous mixture of water miscible solvents, a nitrile solvent, and a hydrocarbon solvent.

26. (Withdrawn) The process of claim 25, wherein said ketone solvent is selected from the group consisting of acetone, methyl ethyl ketone, 2-pentanone, and a mixture thereof.

27. (Withdrawn) The process of claim 25, wherein said aqueous mixture of water miscible solvents comprises a C_1-C_5 straight or branched chain alcoholic solvent.

28. (Withdrawn) The process of claim 27, wherein the straight or branched chain alcoholic solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, 2-butanol, n-butanol, n-pentanol and 2-pentanol.

29. (Withdrawn) The process of claim 25, wherein said nitrile solvent is acetonitrile or propionitrile.

30. (Withdrawn) The amorphous levocetirizine dihydrochloride produced in accordance with the process of claim 19.

31. (Withdrawn) The amorphous levocetirizine dihydrochloride produced in accordance with the process of claim 22.

32. (Withdrawn) The amorphous levocetirizine dihydrochloride produced in accordance with the process of claim 25.

33. (Withdrawn) A pharmaceutical composition comprising i) a prophylactically or therapeutically effective amount of amorphous levocetirizine dihydrochloride in a solid form produced by the process of claim 19, and ii) one or more pharmaceutically acceptable excipients.

34. (Withdrawn) The composition of claim 33, wherein said pharmaceutical composition is a solid dosage form for oral administration.

35. (Withdrawn) The composition of claim 34, wherein said solid dosage form is a tablet.

36. (Withdrawn) The composition of claim 33, having a moisture content ranging from about 0.3% to about 12% by the KF method.

37. (Withdrawn) The composition of claim 33, having a moisture content ranging from about 1.5% to about 7.5% by the KF method.

EVIDENCE APPENDIX

A copy of the article by O. Almarsson and C. R. Gardner, “Novel Approaches to Issues of Developability,” *Current Drug Discovery,* January 2003, pp. 21-26, cited by appellants during prosecution, is attached.

An eight-page website reprint of the article by A. Goho, “Tricky Business,” *Science News*, Vol. 166, pages 122-3 (August 21, 2004), cited by appellants during prosecution, is attached.

RELATED PROCEEDINGS APPENDIX

None.

Novel approaches to issues of developability

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TransForm Pharmaceuticals Inc, USA

Considerations of developability, such as 'is the compound drugable', are often left until a lead is selected for trials. Investigating the form and formulation of compounds at the early preclinical stage can save significant costs and time. Here we take a look at how to ensure your candidate is a suitable drug using high-throughput form and formulation technologies.

In recent years, several new technologies have been developed which have enabled great strides in the generation of lead compounds for development into pharmaceuticals. First, the genomic revolution cast a floodlight on the diversity and expression of putative targets for drug discovery. Second, the advent of combinatorial chemistry produced vast libraries from which discovery groups could initiate searches for compounds active at new targets. Third, *in vitro* potency and selectivity assays have become automated with newly available commercial equipment, which is increasingly user-friendly to laboratory personnel. Automation in preclinical research (including metabolic profiling and permeability screening) has facilitated identification of membrane-permeable molecules, the metabolism of which can be characterized at a fairly early stage. These advances were in all cases made possible by high-throughput (HT) methodologies.

Despite this progress, the drug industry finds itself in a productivity crisis as the number of new drugs registered has not kept pace with the increased resource expenditures in discovery. Two elements that exacerbate the issue are the increasing chemical complexity of compounds in discovery and the lack of available technologies to deal with the increased output of compounds downstream of discovery. Increased chemical complexity is a result of advances in genomics and combinatorial chemistry; there are more plentiful targets that require increasingly elaborate molecules to selectively address the intended target. Combinatorial chemistry has led to the generation of compounds that have progressively more challenging properties; an acute lack of water solubility, as well as poor dissolution characteristics, are frequently a problem in early development.

What is developability?

'Developability' refers to the quest for desirable properties beyond the classical focus on potency and selectivity, ie, does a compound have the desirable pharmaceutical properties to make a drug? The key to efficiently traversing the preclinical stage of drug development involves the marriage of classical criteria with consideration of developability. Limitations of developability raise significant hurdles for advancing compounds into the clinic and for this reason, preclinical development is showing signs of becoming a bottleneck. Due to the mounting pressure on development groups to bring challenging compounds forward to proof-of-principle studies in the clinic, new technologies and capabilities are needed to accelerate preclinical evaluation. In order to increase the chances of identifying a compound with suitable physical properties and advancing it to development, HT techniques are now being devised for the preclinical space.

Two questions are beginning to receive attention across the pharmaceutical industry and they provide the focus of this article: Why is consideration of pharmaceutical properties becoming increasingly critical to drug discovery and preclinical development? And, what HT strategies help to address developability at earlier stages, when amounts of test substance are often limiting?

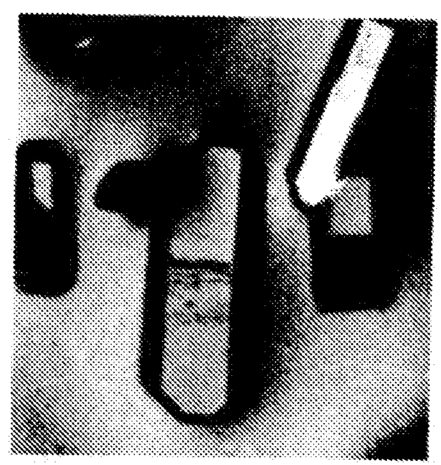

Figure 1. The form of a drug candidate is a critical attribute that determines the physical properties of the compounds and significantly affects pharmaceutical processing, stability and bioavailability.

The importance of physical form

To address the question of why consideration of pharmaceutical properties is becoming increasingly critical to drug discovery and preclinical development, one must consider the importance of physical form (Figure 1). Form determines function; this statement is true in the world of materials in general. For instance, the differences in properties between a crystalline and a non-crystalline (amorphous) compound are easily recognizable in terms of density, hardness, stability to stress, etc. The properties of a drug product are determined by the materials that it contains. Therefore, an active molecule must be converted into a pharmaceutical material in order to make it useful to the patient. Nevertheless, form definition (the selection of the optimal crystal form of a drug substance) and formulation activities to prepare the compound for toxicology and ultimately human studies are sometimes seen as 'necessary evils' in advancing a candidate compound from discovery to clinical development. Due to lack of available material, there is conscious prioritization of its use in the biological assays, pharmacokinetic evaluation and pharmacological studies in animals. Few resources are typically allocated to physical characterization of early stage compounds but, as a consequence of poor definition of the physical nature of the candidate compound, a discovery-to-development transition may stall due to problems with the solid form of the substance and hence the formulation options that are available. Let us consider two issues of developability that are commonly faced in the corridor leading from discovery to early stages of drug development: amorphous materials and insoluble, poorly-absorbed compounds.

Amorphous materials

Discovery programs frequently yield amorphous compounds due to time pressures and the methods used to isolate them on small scales. In addition, lead compounds have evolved in terms of their structural complexity, and hence crystallization is a challenge that often awaits the involvement of pharmaceutical and process chemists. Examples of amorphous compounds that have persisted through development and reached the market are listed in Table 1.

> ***"...a major driver for early consideration of pharmaceutical properties is the mounting formulation challenge in preclinical development."***

Amorphous compounds carry inherent risks due to their physicochemical nature. In addition to being physically meta-stable (ie, prone to physical form changes such as crystallization), amorphous forms are generally less chemically stable in the solid state than the crystalline form. Amorphous compounds also tend to have very low bulk densities, making the materials difficult to isolate and handle. They also exhibit irregular particle properties and their high surface area often results in hygroscopicity (excessive moisture-sorption). These properties, despite presenting a potentially surmountable set of issues in discovery and early development, can cause major challenges in late-stage development.

In general, pharmaceutical companies make every effort to avoid committing to the development of an amorphous compound. When sufficient quantities of such a compound become available, development scientists may obtain a crystalline form, the solubility of which can be dramatically (up to orders of magnitude) lower than that of the amorphous form. The decreased solubility frequently compromises or even abolishes oral absorption from the solid-state. This unsatisfying predicament leads to major resource expenditures in formulation development to recover *in vivo* performance. The resulting formulations often do not meet the criteria of chemical stability and processability, and hence the resulting dosage forms may limit the progress of a clinical program. As has already been stated, amorphous forms have, in rare cases, been chosen for development despite the risk of crystallization, an event that could cause a product to fail its critical performance criteria and regulatory specifications. The results of such an occurrence are disastrous for development programs, especially in late-stage trials where the formulation used is that intended for the market.

Insoluble poorly-absorbed compounds

In those cases where a crystal form exists but has poor or non-existent bioavailability, significant effort is often spent finding formulations that improve absorption characteristics. Frequently, an innovator

Drug product	Drug substance	Molecular weight	Therapeutic class and use
Accupril®	Quinapril HCl	439	ACE inhibitor for hypertension
Accolate®	Zafirlukast	576	Leukotriene antagonist for asthma
Viracept®	Nelfinavir mesylate	568	HIV protease inhibitor for AIDS

Table 1. Examples of FDA-approved products based on amorphous drug substances.

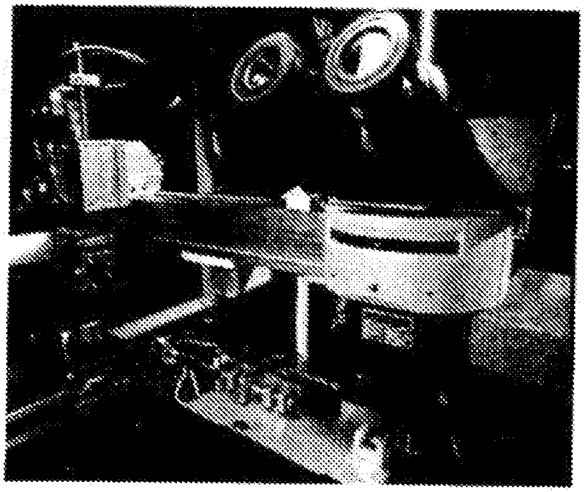

Figure 2. An automated Raman microscope is a central part of high-throughput crystallization, enabling rapid characterization and classification of novel solid forms of drug candidates.

company may be in this situation because a compound that was previously amorphous and well absorbed in early animal studies was converted to a much less bioavailable crystalline state in the development phase. Although oral solutions may overcome poor oral absorption, such an approach is generally not considered ideal due to stability and user acceptance concerns. For instance, taste considerations can adversely affect the progress of a clinical program and marketing groups are usually averse to the idea of an oral solution product as their major marketed dosage. Strategies to improve absorption without resorting to a solution formulation include formation of a salt or the creation of dispersions, both of which aim to increase dissolution rate of the compound, thus enabling improved oral absorption.

Occasionally, suitable salt forms of acidic or basic compounds are not obtained, despite significant efforts in salt selection. Molecular dispersions, such as a solid-solution of drug in a semi-solid matrix or suspensions of nanometer-sized test substance with surfactants and other suspending aids, share some of the same stability risks as amorphous compounds: over time, and generally in an unpredictable fashion, nucleation and/or growth of crystalline particles may take place. As a result, the level of compound solubility or dissolution rate that was previously recorded in the medium is lost with adverse consequences for the bioavailability. The development of dispersions is therefore challenging and risky.

Clearly, a major driver for early consideration of pharmaceutical properties is the mounting formulation challenge in preclinical development. The issues of amorphous compounds and poorly-absorbed crystalline forms raise the specter of increased complexity of dosage form development, which is unpalatable to pharmaceutical companies in an increasingly competitive industry where speed to market is critical. If the issues are not addressed successfully early on in the pre-clinical stage, the compound may fail or become sidelined in order to progress another candidate that satisfies formulation criteria including developability and the desires of marketing groups. Because a compound in the formulation stage is relatively far along in preclinical development, the opportunity costs associated with dropping the compound for lack of ability to formulate (developability) are quite significant.

Form and formulation opportunities

What HT strategies can be brought to bear to address form and formulation (F&F) issues encountered in preclinical drug development? One way to preempt problems of developability without a substantial increase in resources is to apply HT technologies in the following areas:

- Crystallization of amorphous compounds (identification of a stable physical form)
- Salt selection (when salt forms are required to optimize performance)
- Preformulation (solubility, stability and compatibility of crystal forms with potential formulation components)
- Formulation (eg, liquids or suspensions for toxicology and proof-of-principle human studies)

Two major challenges to overcome in the design and implementation of HT F&F technologies are: (i) the need for specialized equipment for dispensing and analysis; and, (ii) the limited availability of test material. On the equipment side, one must be able to handle a range of materials, including non-aqueous, viscous liquids and semi-solid materials and because only a limited selection of commercial equipment to handle such a range of properties simultaneously is available, significant customization is inevitable. Analysis equipment may include sophisticated vision systems and spectroscopic techniques that need to be custom-fitted to allow in-line analysis of crystals or formulations.

The lack of available material is another major impediment to application of HT in discovery or at the discovery-development interface, since at this stage the bulk of a given compound that is advancing toward candidate selection is funneled into animal experiments. It is difficult to justify the cost of scaling up syntheses of discovery phase compounds, most of which will not have much value beyond discovery. Generally, a diversity of molecules is required in the early days to establish the structure-activity relationships and because common intermediates are used to prepare such compounds, the stock of the intermediate at any time is limited. Therefore, in order to move F&F research toward lead optimization support, one must learn how to do more, with less material from the discovery phase. For example, the search for crystal forms and salts of compounds emerging from discovery must rely on automation and miniaturization of crystallization trials. Currently, development chemists may experiment with 1-10 mg per trial on a total budget of 10s to 100s of milligrams. Although material is usually recoverable at a cost in time and effort, the traditional experimentation remains linear in nature. The search for crystal forms in such a linear fashion is time-consuming, and all the while the pressure mounts to test a compound in toxicology and the clinic. The technical solution provided by HT crystallization is the possibility of parallel, miniaturized trials of a

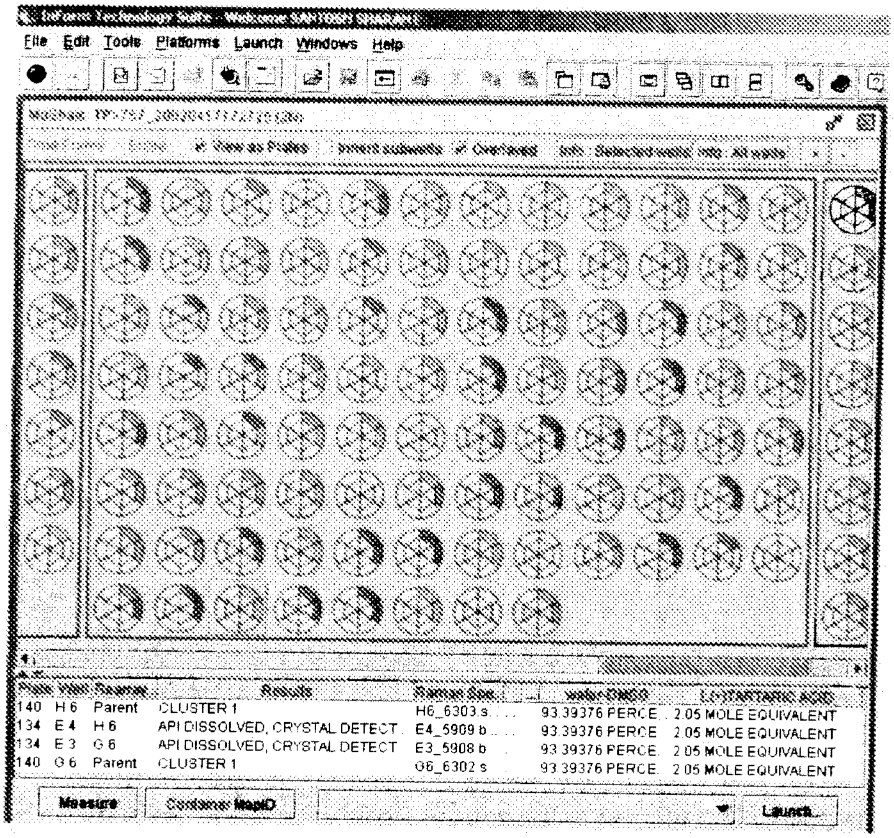

Figure 3. Informatics software allows the analysis of high-throughput F&F screening data to identify leads for preclinical evaluation and dosage form development for clinical studies.

larger experimental space (solvents, combinations, processing parameters, and so on). In order to meaningfully increase the productivity of crystallization efforts, one must be able to conduct parallel experiments at the level of micrograms per trial. In this way, valuable time and material can be saved, while generating useful physicochemical information to support development decisions. For instance, if crystalline forms are found, the program can confidently move forward to assessing their utility.

Even when a crystal form remains elusive, the information from crystallization trials on the compound and some of its congeners may help the medicinal chemists design the optimal compound to advance the program. Also, the inability to crystallize a compound in a large number of parallel trials can sometimes give a scientists working on a program sufficient confidence to use an amorphous form (even though the absence of crystalline material in HT experiments can never disprove the existence of a crystal form entirely). Downstream of discovery, the issue of polymorphism, which is defined as the presence of distinct crystalline forms of a given compound, becomes a technical and regulatory challenge, an important example of which will be provided towards the end of this article. HT crystallization screening provides a way to address polymorphism issues much earlier and can help to avoid late discoveries of polymorphism in pharmaceutical systems.

TransForm HT technology

Through significant investment in automation and informatics, TransForm Pharmaceuticals has developed distinctive F&F HT platforms, including an HT crystallization technology called CrystalMax™, which enables parallel, miniaturized crystallization of compounds in cycles of 1- to 2-weeks (Figures 2 and 3). Iterations are possible, indeed desirable, and a database tracks all transactions relating to every experiment. Visualization and analysis of data from the database is a key feature that enables decision-making regarding form selection. The technology allows design, execution and analysis of thousands of crystallization trials on 100s of micrograms of crystalline material per well in microliter volumes within a 96-well array format. Much of the CrystalMax™ technology platform is custom-made, since off-the-shelf solutions are not considered adequate. For instance, current systems suffer from incompatibilities with handling of a vast variety of volatile organic solvents used to produce crystal diversity. One of many examples of the success of the new platform is shown in a recently published study of the crystal polymorphism of the well-known drug acetaminophen (paracetamol) (Peterson ML *et al*).

FAST™ is an HT technology that was developed to discover novel solution formulations of poorly soluble compounds, either for intravenous or oral use. The technology uses 96-well format to conduct parallel screening of thousands of combinations of semi-aqueous formulations. Another formulation technology, SFinX™, has been developed to discover excipient combinations that dissolve poorly water-soluble compounds for oral delivery. As part of the process, non-aqueous concentrates are presented to an *in vitro* dissolution test in 96-well plates, in order to assess the physical form of the drug that will be produced upon dilution in GI tract. These results can be used to predict impact on oral bioavailability. TransForm is applying the above breakthrough technologies in partnerships with major pharmaceutical companies that have recognized the value of early intervention in the area of F&F.

Pharmaceutical companies are considering their options to enhance efficiency in F&F research, either by expanding their capabilities internally, purchasing tools or by outsourcing HT experimentation with pharmaceutical materials. A handful of technology companies are positioning themselves to provide HT crystallization automation tools (Symyx Technologies, Crystallics, Solvias) in the preclinical space.

Impact points

Increasingly, compounds are stalling in development due to issues of form and formulation, and these problems were likely already evident in the discovery phase. Others experience unanticipated biopharmaceutical problems in development or, worse, on the market. The emerging way to avoid these problems is to conduct miniaturized experiments earlier combined with informatics-aided analyses of solubility, solid form diversity, formulation options and biopharmaceutical data. The vision of cross-correlating physical, chemical and biological information for diverse chemical structures is shared by a number of pharmaceutical companies that operate with ever growing sample collections. At present, the best examples of the value of understanding the nature of compounds are historical ones. The examples chosen come from analysis of the pharmaceutical issues with HIV protease inhibitors.

Many will realize that the tremendous strides made in HIV therapy due to the advent of the protease inhibitors in the mid 1990s would not have occurred without the knowledge and experience gained a half a decade earlier, when several companies were deeply involved in the discovery of renin inhibitors. The latter class of compounds largely comprise peptidomimetics, which are compounds that frequently possess the challenging properties of poor aqueous solubility and metabolic instability toward cytochrome P450 enzymes. These issues are prominent in the HIV protease inhibitor class. The types of marketed formulations in this class illustrate the problems that exist with achieving bioavailability (Table 2). In essence, the oral dosage forms consist of drug in an oily solution within soft gelatin capsules or more water-soluble (and in one case amorphous) salt forms in hard gelatin capsules. There were significant challenges along the way to achieving these formulations. Two examples of high-profile problems relate to saquinavir (Invirase® and Fortovase®) and ritonavir (Norvir®).

"HT crystallization screening provides a way to address polymorphism issues much earlier and can help to avoid late discoveries of polymorphism in pharmaceutical systems."

It is well known that the utility of saquinavir, the first HIV protease inhibitor on the market, was severely impeded by poor bioavailability. Because bioavaililty and pharmacokinetics are crucial determinants of the activity of an anti-infective drug, the original formulation, Invirase showed only modest market performance at its peak. Invirase soon became overshadowed by drugs such as ritonavir (Norvir) and indinavir sulfate (Crixivan®) that had better bioavailability. Three years after initial approval, saquinavir was re-introduced in a formulation with six-fold higher oral bioavailability relative to the original product. By extensive F&F effort, the new formulation, Fortovase, was engineered in such a way as to emulsify the drug more effectively in gastric fluid than was possible before. One can surmise that having the better performing formulation at the outset could have enhanced saquinavir's market penetration by mitigating the issue of poor bioavailability of the original formulation.

Ritonavir was originally launched as a semi-solid dosage form, in which the waxy matrix contained dispersed drug in order to achieve acceptable oral bioavailability. In 1998, two years after its introduction, ritonavir exhibited latent crystal polymorphism, which caused the semi-solid capsule formulation of Norvir to be removed from the market. The new drug crystal form did not have sufficient solubility in the formulation and the product therefore began failing dissolution specifications. Knowledge of the crystal form diversity of ritonavir would likely have averted this painful experience. A new formulation was developed; a soft-gelatin capsule containing a liquid excipient mixture in which the new crystal form is soluble.

The storage label for Norvir capsules indicates refrigeration of the drug prior to dispensing to the patient. The same is

HIV Protease	Products	Oral formulation(s)
Saquinavir	Invirase®[1]	Hard gelatin capsule containing the mesylate salt form
Saquinavir	Fortovase®[2]	Soft gelatin capsule containing the free base drug form
Indinavir	Crixivan®	Hard gelatin capsule of the crystalline sulfate salt
Ritonavir	Norvir®	Soft gelatin capsule; oral solution
Amprenavir	Agenerase®	Soft gelatin capsule; oral solution
Nelfinavir	Viracept®	Hard gelatin capsule of the amorphous mesylate salt
Lopinavir	Kaletra®[3]	Soft gelatin capsule; oral solution

[1] Original product.
[2] Improved product with 6-fold bioavailability relative to Invirase®.
[3] Formulated as a fixed-dose combination of Lopinavir with Ritonavir.

Table 2. FDA-approved HIV protease inhibitors.

true for the recent combination protease inhibitor, lopinavir (Kaletra®) (Table 2). The late discovery of crystal polymorphism of ritonavir is another example of a disaster that might have been averted by early HT study of crystal forms of the compound.

Developability moving forward

One can envision a future when the developability of a scaffold or drug class is known well in advance of lead optimization and preclinical research. The key to interfacing early in discovery will be the ability to work with microgram amounts of substance, advanced design of experiments with sophisticated informatics, and high-speed analysis to create valuable information across compound series and even an entire sample collection. Database capture of pharmaceutics from HT experimentation, and the knowledge that will emanate from coupling developability data with biological data, gives rise to boundless possibilities to accelerate drug discovery and development.

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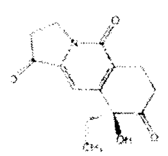
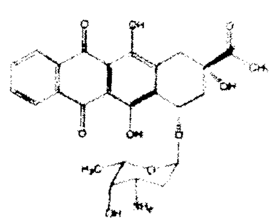




Science News Online
Week of Aug. 21, 2004; Vol. 166, No. 8

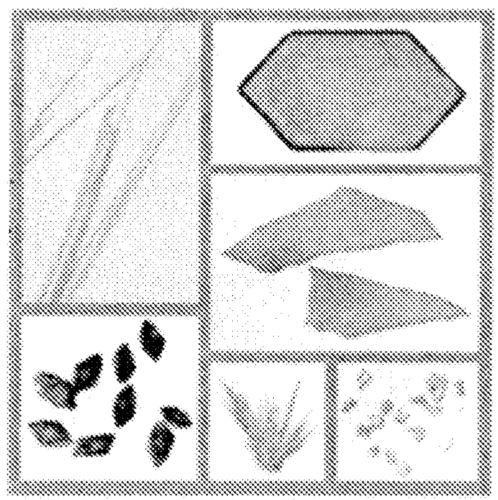
Tricky Business

The crystal form of a drug can be the secret to its success

Alexandra Goho

In one of Kurt Vonnegut's science fiction novels, a scientist creates a form of ice that doesn't melt until it reaches 114.4°F. Called Ice-9, this imaginary crystal takes over the world, as all of Earth's waters, and life itself, freeze solid. What endows Ice-9 with such unusual properties is the unique configuration of the stacked water molecules. Although Ice-9 of *Cat's Cradle* (1963, Holt, Rinehart and Winston) is pure fantasy, the concept of a molecule assuming multiple crystal structures—or polymorphs—is real, and the consequences can be dramatic. One polymorph of carbon provides black and slippery graphite, another is hard, transparent diamond. A blue pigment used in ink-jet printers has either a red or green tint, depending on the pigment's crystal structure. Even crystallized cocoa butter has different polymorphs; some cause the chocolate to melt in your mouth more quickly than others.

In recent years, the pharmaceutical industry has increasingly focused its attention on polymorphs. There's plenty of incentive. The precise arrangement of molecules within the crystal of a drug determines how fast it dissolves in the body and how much enters the bloodstream. Polymorphs of a drug differ in properties that affect its shelf life or ease of manufacture. A newly discovered polymorph may turn out to be a more effective and convenient than the original product.



TRUE COLORS. The organic compound dubbed ROY can adopt six different crystal structures, or polymorphs, ranging from yellow needles to orange-red plates. ROY is currently the world record holder for having the largest number of fully characterized polymorphs.
Yu

The Food and Drug Administration requires all companies to register the precise polymorph of any drug that they produce. Pharmaceutical manufacturers also have to demonstrate that each polymorph is stable and can be reproduced reliably. Otherwise, it would be hard to set a drug's effective dosage. "The FDA has very strict regulations on this," says Jerry Atwood of the University of Missouri-Columbia.

Regulations aside, drug companies are becoming increasingly aware that different polymorphs can translate into more or less profit. Because each polymorph is legally defined as a unique, patentable composition of matter, a company that develops a new drug will patent all the polymorphs that it has discovered and produced.

That, however, affords the patent holder only limited business protection. Because the science behind polymorphs remains murky, there's no guarantee that a competitor won't discover a new polymorph of the drug that's better than the patented ones.

The world of polymorphs also opens up complicated business strategies. For example, when a patent is set to expire, a company might have other patents related to a drug's polymorphs that make it difficult for competitors to produce generic versions.

Situations such as these have fueled intense litigation over the years. "The polymorph issue is so important to the pharmaceutical industry," says Atwood. "We're talking about multibillion-dollar drugs. Ultimately, it comes down to a hard legal battle."

It also comes down to fundamental chemistry. Polymorphism has elicited enough excitement and fear in the drug business that a growing number of researchers in academia and in private companies are taking a closer look at how crystals grow, and what these scientists discover could shape an entire industry.

Disappearing act

Emblematic of the importance of polymorphs is the cautionary tale of ritonavir, the AIDS drug made by Abbott Laboratories. Introduced in 1996, the drug had been on the market for 18 months when suddenly, during manufacturing, chemical engineers detected a previously unknown polymorph. No one knew what had caused the change, but the scientists discovered that the new polymorph was thermodynamically stabler than the drug in its original form. The Abbott team couldn't find a way to stop formation of the new polymorph. Within a few days of its discovery, this new polymorph was dominating the product coming off the lines, says Sanjay Chemburkar, one of the Abbott chemists involved in the situation.

Although the two polymorphs shared a chemical formula, their structural dissimilarity made a difference to patients. The second form was only half as soluble as the first, so patients taking prescribed doses wouldn't get enough of the drug into their bloodstreams. Abbott pulled ritonavir from the market.

"The company went on a crash program to try to get their [original] polymorph back," says Atwood. Abbott eventually succeeded in producing the first form again, but it could not make the polymorph reliably and kept getting mixtures of the two forms. The company finally decided to reformulate the drug in the second polymorphic form as a liquid gel capsule containing the predissolved drug. Unlike the original formulation of the drug, the gel capsules require refrigeration.

"Abbott lost a lot of money over this," says Allan Myerson of the Illinois Institute of Technology in Chicago. The company spent hundreds of millions of dollars trying to recover the first polymorph and lost an estimated $250 million in sales the year the drug was withdrawn.

Cases such as this aren't routine, but they're common enough for drug companies to be concerned about the surprises that polymorphism can bring, says Myerson.

Screening for polymorphs early on is always best, says Patrick Stahly. He's the chief operating officer at SSCI, a contract research laboratory in West Lafayette, Ind., that specializes in crystal screening and analysis. Even so, drug companies often wait until late in the development process before thoroughly screening for polymorphs. "We've had clients come to us in the middle of human clinical trials after discovering their drug had two different polymorphs," says Stahly. Such a company has to regain control over its manufacturing

process and start the trials over using a single polymorph.

That experience underscores one way that companies can get bitten by polymorphism. There are other potential pitfalls as well.

Consider ranitidine hydrochloride, the anti-ulcer drug owned by the drug giant GlaxoSmithKline and known by millions as Zantac. In the mid-1990s, as the patent on the drug was approaching expiration, other companies began gearing up to market cheaper, generic versions. By marketing drugs that have gone off patent, generics manufacturers skip human trials, the most expensive part of the drug-development process.

However, GlaxoSmithKline—which was simply Glaxo at the time—had in its pocket a patent on a second polymorph of the drug. The company discovered that second form early in the processing of the first form. Glaxo didn't receive a patent on the second form until nearly 7 years after receiving the initial drug patent. Because the second form was easier to manufacture, it became the active ingredient in Zantac.

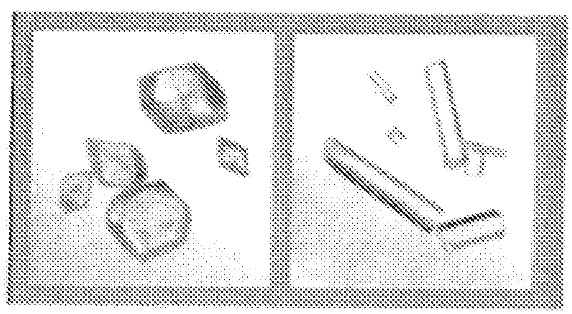
Although other companies were legally permitted to make and sell generic versions of the first polymorph of ranitidine hydrochloride, they had to figure out how to make it without any contamination from the second, whose patent protection remained in force. This kept the generic companies products off the market for several years.

"Zantac was the largest-selling drug in the world," says Joel Bernstein of Ben-Gurion University of the Negev in Beer Sheva, Israel. Bernstein was an expert witness for Glaxo when a dispute over its original patent went to court. Glaxo was making $10 million in sales each day on its ulcer treatment, so every day it retained control over its drug was significant.

Crystal fate

The conventional approach to finding polymorphs begins with old-fashioned crystallization experiments. First, dissolve the drug in a solvent. Next, cool the solution or evaporate the solvent, coercing the drug molecules to stick together to form crystals. Varying the temperature of the solution and using different solvents are among the long-used tricks for getting the molecules to stack in different geometries.

Trying to discover new polymorphs in the lab can be frustrating. "Sometimes they show up, sometimes they don't," says Adam Matzger of the University of Michigan in Ann Arbor. "There is very little in the way of new approaches to finding polymorphs."



POLYMER RELIEF. Growing crystals of the pain-relieving drug acetaminophen on different polymer surfaces will yield different crystal structures. One polymer gives rise to tiny prisms (left); another, miniature monoliths (right).
Z. Tolstyka

In search of ideas, researchers have been exploring factors other than temperature and solvent that might influence crystallization and produce polymorphs. For instance, SSCI is investigating a technique developed by Myerson. Two years ago, he and his colleagues found that intense pulses of near-infrared light could affect the crystallization of the amino acid glycine. When the light was linearly polarized, so that its

electric field vibrated in one direction, the crystal grew as one polymorph; when the light was circularly polarized, so that the electric field rotated, it induced a second polymorph.

Myerson suspects that the electric field generated by the light influences how the glycine molecules arrange themselves as they aggregate into small clusters early in the crystallization process.

The instructions for growing into a particular type of polymorph are imprinted on the cluster by the time it reaches a critical size containing tens to hundreds of molecules. Once these nuclei form, the "fate of the system has been decided," says Michael Ward of the University of Minnesota in Minneapolis.

Different packings of molecules lead to nuclei of different sizes, which in turn yield different polymorphs. So, Ward wondered whether confining a dissolved compound to a given space would limit the size of a nucleus that could form and force the molecules to pack in a specific polymorphic arrangement. As they reported in the March 24 *Journal of the American Chemical Society*, he and his colleagues tested this hypothesis by growing crystals within porous materials.

The Minnesota team turned to blocks of polymer with cylindrical pores 30 nanometers in diameter. To this material, the researchers added a solution of an organic chemical commonly used in the manufacture of pharmaceuticals. This compound, dubbed ROY, is currently the world record holder for having the most—six—fully characterized polymorphs. However, Ward and his colleagues found that only one form of ROY crystallized inside the pores.

Ward notes that the fine details of surfaces also play a role in crystallization. Think of rock candy. "When you dissolve sugar in water and put a stick in the container, where does the candy grow? On the stick," he says.

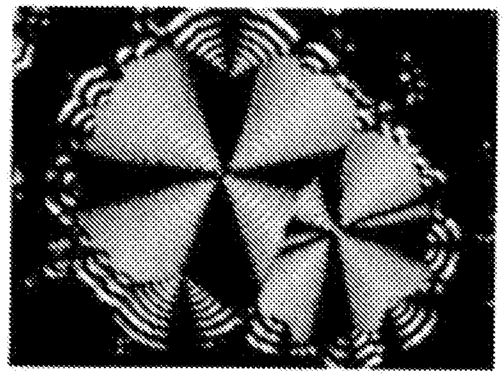
Matzger, for one, has found that growing crystals of the same compound on different polymer materials can produce different polymorphs. The Michigan group crystallized the pain-relieving drug acetaminophen, which is known to have two polymorphs, on 84 different polymer materials. They found that certain materials, such as nylon and polyvinyl chloride—the plastic used in plumbing—induced one form to grow, while other polymers, such as cellulose, favored the other form.

Next, the researchers did a similar experiment with carbamazepine, an antiepileptic drug with three known crystal structures. Not only did all three polymorphs show up, but also a new and previously unknown polymorph grew on 4 of the 84 polymers. Matzger speculates that the precise way in which a polymer's atoms are arranged near the surface could favor the growth of certain polymorphs.

While pharmaceutical firms might use strategies like these to discover new polymorphs, once a company lands on a desirable crystal form of a drug, it faces other challenges. To make large quantities, researchers often seed batches of the dissolved drug with a small grain of the desired polymorph, expecting the grain to nucleate the growth of much larger crystals of the same polymorph.

That strategy usually works, but sometimes it doesn't.

"The engineers will often say to me: 'The polymorphism of this drug is out of control. I seed with this crystal and I get something else,'" says pharmaceutical chemist Lian Yu.



BAD SEED. Two different polymorphs of the sugar mannitol were detected with a spectral-imaging technique. The two crystal structures scatter radiation differently, producing a unique pattern of black and white bands. The image shows how one polymorph of mannitol (inner pattern) can cause a second polymorph (outer pattern) to grow on its surface.
J. Am. Chem. Soc.

While working at Eli Lilly and Company in Indianapolis, Ind., Yu discovered that the surface of one crystal structure sometimes induces a different polymorph. In the May 28, 2003 *Journal of the American Chemical Society*, Yu describes an experiment in which he used a polymorph of the sugar mannitol to seed a dissolved solution of the sugar. The polymorph that started forming on the surface of that crystal was a different one altogether.

Yu, who is now at the University of Wisconsin–Madison, suspects that this process could be at the heart of many incidents, such as Abbott's ritonavir saga, in which researchers at drug-manufacturing plants suddenly find they can no longer grow the polymorph they want. Some unrecognized change in the manufacturing process might have altered whether the growing crystals model themselves after their seed crystals.

Forecasting

In 1965, a Chicago microscopist named Walter C. McCrone stated the following maxim regarding the art of crystal growing: "The number of forms known for a given compound is proportional to the time and money spent in research on that compound."

Consider ROY. It took Yu and his colleagues many years to produce all six forms, which they first reported in 2000. The colorful diversity of the different crystal structures—which range from red needles to orange plates to yellow prisms—and the fact that they all form at room temperature "really has captured the imagination of the community," says Yu.

Other compounds, however, do not support McCrone's rule. Aspirin, for example, has been crystallized by the tons for decades under many different conditions, and yet only one crystal form has ever emerged, says Sally Price at University College London. "People are fairly confident that there aren't any more to be found," she says.

Yet without extensive studies, there is no way to entirely discount the possibility that some sets of conditions could lead to polymorphs of aspirin. "Right now, you can't predict polymorphs, and you can't predict their properties," says Atwood.

Such forecasting might be possible in the future. Last fall, Price and her collaborators launched a multimillion-dollar research initiative to develop computer software tools that consider the arrangement of atoms within a compound to predict whether that compound is likely to take on different crystal structures and, if so, approximately how many.

A company might use such predictions to find that one of its drug molecules has other stable polymorphs. If so, the company would aggressively search for those polymorphs. The

predicted crystal structures would also give researchers ideas for methods to produce the polymorphs in the lab.

Alternatively, the predictions might suggest that the polymorph in hand is the stablest form and that other forms are unlikely to arise. The company could then save the time and money that would otherwise be spent on unnecessary screening experiments.

At the moment, Price says her team can make predictions only for very simple molecules. "Most pharmaceuticals are far more complicated," she says. It could be a decade before such computer predictions can be applied to drug development. In the meantime, the specter of sudden polymorphism will remain a fact of life for pharmaceutical firms.

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From *Science News*, Vol. 166, No. 8, Aug. 21, 2004, p. 122.